1965

Respiration in Dogs with Spinal Cord Transection at C1

Peter Joseph Kane
Loyola University Chicago

RESPIRATION IN DOGS WITH SPINAL CORD TRANSECTION AT C1

by

Peter Joseph Kane, Jr.

A Thesis Submitted to the Faculty of the Graduate School of Loyola University in Partial Fulfillment of the Requirements for the Degree of Master of Science

JUNE

1965

ACKNOWLEDGMENTS

The author wishes to express his sincere gratitude to Dr. Walter C. Randall and Dr. Clarence N. Peiss, his advisors, for counsel, encouragement and guidance in the preparation of this thesis. He also wishes to express his thanks to his wife for assistance in the writing of this thesis.

BIOGRAPHY

Peter Joseph Kane, Jr. was born in Evergreen Park, Illinois, February 18, 1941. Following graduation from St. Sabina Grammar School, Chicago, Illinois, in 1954, the author attended St. Columban's Minor Seminary at Silver Creek, New York, for three years. He entered Leo High School, Chicago, Illinois, in September, 1957, and graduated "cum laude" in June, 1958.

The author was awarded an Illinois State Scholarship to the College of Arts and Sciences of Loyola University from 1958 to 1961. While in college, he became a member of the Pi Alpha Lambda Fraternity.

In 1961, the author entered the Stritch School of Medicine of Loyola University and began work leading to the degree of Doctor of Medicine, and will be graduated "cum laude" on June 8, 1965. The author began graduate studies in the Department of Physiology of Loyola University in September, 1962. In July, 1964, he was awarded the Royal E. Cabell research fellowship. While in Medical School, he was a member of the Student American Medical Association and was awarded a Pre-Clinical Honors Certificate.

The author was married to Patricia Anne Robertson on October 10, 1964.

TABLE OF CONTENTS

Chapter		Page
	ACKNOWLEDGMENTS	i
	BIOGRAPHY	ii
	TABLE OF CONTENTS	iii
	LIST OF FIGURES	iv
I.	INTRODUCTION	1
II.	MATERIALS AND METHODS	6
III.	EXPERIMENTAL RESULTS	11
IV.	DISCUSSION	20
V.	SUMMARY	27
	BIBLIOGRAPHY	29

LIST OF FIGURES

Figure		Page
1.	Spontaneous Respiration Superimposed on Respiratory Pump	13
2.	The Influence of Hypoxia on Respiratory Rhythmicity	16
3.	Phrenic Nerve Activity Correlated with Changes in Abdominal Circumference	18
4.	Blood Pressure before and after Spinal Transection	23

CHAPTER I

INTRODUCTION

Since it is known that the isolated spinal cord is capable of regulating to a greater or lesser degree vasomotor, sudomotor, and somatic reflex activity, the question arises as to whether the isolated spinal cord is also capable of regulating respiratory activity. Many years ago Galen (1) observed that following high transection of the cervical spinal cord respiration was instantly abolished. This fact was later confirmed by Lorry in 1760 (2). Brown-Sequard (3) however postulated the theory of long inhibition of respiration as a result of trauma in order to explain the cessation of respiration following separation of the phrenic nerve nuclei from the bulb. Rokitansky (4) reported that in young rabbits treated with strychnine following transection of the cervical spinal cord between C1 and C2 he had observed respiratory activity amidst convulsions. Langendorff questioned the interpretation of Rokitansky's work and the significance of recordings obtained amidst convulsive activity. In 1880 Langendorff (5) performed a series of experiments on cats and rabbits to ascertain the effectiveness of the spinal cord in initiating respiratory

activity. Using animals only a few days old he performed a high cervical transection of the spinal cord and maintained the animals on artificial respiration. He then administered a dose of .5 - 1.0 mg of strychnine intramuscularly. Following a period of convulsions of unknown duration he discontinued the artificial respiration and observed the establishment of rhythmic respiration once the period of convulsions had passed. In his experiments Langendorff's only measure of respiratory activity was a curve of intrathoracic pressure changes. This he obtained by means of a Marey Tambour connected to the end of the tracheal cannula. He then attempted to record respiratory activity without the use of strychnine but was unsuccessful except when using very young animals not more than one or two days old.

Wertheimer in 1886 (6) confirmed the observations of Langendorff. In addition, he claimed that it was possible to reestablish respiration in adult animals without the use of strychnine following transection of the cervical spinal cord. He stated that in young animals this function returned more readily than in adult animals because the younger animals were able to withstand the surgical trauma better. In his experiments, he, like Langendorff, measured intrathoracic pressure by means of a Marey Tambour connected to a fifteen liter reservoir interposed between the tracheal cannula and the Tambour. He surrounded the animals with cotton wool in order to keep body temperature fairly constant. He then maintained the animals for 4-6 hours on

artificial respiration. When the artificial respiration was discontinued, he recorded rhythmic changes in intrathoracic pressure lasting for ten or more minutes with no convulsive activity. He stated that he was not able to record spontaneous respiratory activity in animals less than four hours after completion of the transection since trauma to the cord during transection produced a prolonged inhibition of respiration. He attributed the respiratory activity he had observed to the spinal respiratory centers which were stimulated by anoxia.

Porter in 1895 (7) challenged the interpretation of Langendorff's and Wertheimer's work. He challenged the method by which Langendorff and Wertheimer had measured their respiratory activity. To do this he conducted a series of experiments on dogs using a recording system similar to that of Langendorff and Wertheimer. Following a double transection of the cervical spinal cord at the levels of C1 and C5, these animals were maintained on artificial respiration with warmed air. Following interruption of artificial respiration he recorded a series of curves of intrathoracic pressure almost identical to those of Langendorff and Wertheimer. He observed no sign of contraction of the diaphragm but rather strong rhythmical contractions of the sternocleidomastoid and trapezius muscles. He attributed the changes of intrathoracic pressure changes which he measured and also the curves shown by Langendorff and Wertheimer to be a result of the action of the trapezius and

sternocleidomastoid muscles, rather than the diaphragm. He also exposed the diaphragms of six dogs and found that in only one case were contractions seen in the exposed diaphragm following complete transection of the cervical spinal cord and that in this instance the observed contractions did not resemble those of normal respiration. He also cited the work of nine other authors: Friedericq, Kronecker, Marckwald, Grossman, Laborde, Girard, Gad and Marinescu, and Arrheim who made special studies of respiratory activity following separation of the cord from the bulb and found no activity resembling that of normal respiration.

Porter also attacked the hypothesis of long respiratory inhibition following injury to the cord as the explanation for failure to observe respiratory activity following complete transection of the spinal cord. To do this he cited the work of Paul Bert who made a longitudinal section of the cord from near the bulb to the level of the fourth cervical nerve with no interruption of respiration and the work of Nitschmunn who split the entire cervical spinal cord in the median line without interruption.

Hermann in 1936 (8) offered the following explanation of the conflicting reports concerning spinal centers of respiration. He proposed that the localization of the respiratory center was related to the ontogenetic development of the organism. He theorized that the respiratory nervous function is spread diffusely throughout the cerebrospinal system at birth, but as the

development of the organism proceeds the spinal centers will become at first subordinate and then disappear, maintaining the potential to reappear from a functional point of view under special circumstances and in certain cases.

It is generally believed at the present time that the initiation of respiratory activity is a supraspinal phenomenon. In recent reviews Young (9) states that a transection 2 mm caudal to the obex causes cessation of respiration. This is in agreement with Lambertsen (10) who states that following a section at the tip of the calamus scriptorius, complete and permanent paralysis of respiration occurs.

CHAPTER II

MATERIALS AND METHODS

Mongrel dogs of both sexes weighing 8-15 Kg were used for these experiments. Serynlan (2 mg/Kg) was administered intramuscularly to facilitate handling of the animals following which chloroform anesthesia was administered by a face mask. A T-cannula was inserted into the trachea and chloroform administered continuously by a closed positive pressure circle system with 100% oxygen. The femoral artery was cannulated and blood pressure continuously monitored with a Statham P23A pressure transducer connected to a Grass Model 5 polygraph. Atropine sulfate (2-5 mg) was administered intramuscularly to decrease secretions stimulated by Serynlan. The animal was immobilized in a prone position by a head holder. The muscles of the dorsum of the neck were divided and separated by electrocautery. An opening was made in the foramen magnum by a sharp scalpel and the cerebrospinal fluid released by a small incision in the dura mater and arachnoid. Following removal of the cerebrospinal fluid the opening was enlarged by dissection and removal of the dura and arachnoid. After exposure of the dorsum of the cord

0.2 - 0.4 cc of 1% Ravocaine was injected into the dorsum of the cord until a slight swelling of the cord was noticed. A small longitudinal incision was then made in the dorsum of the pia mater by means of a 27 gauge needle following which the periphery of the spinal cord was teased away from the pia mater by careful separation with a fine probe and forceps. The cord was transected at the level of the first cervical nerve by slowly teasing the cord apart over a period of 30-45 minutes. This procedure was utilized rather than laminectomy in order to avoid the bleeding problems associated with the latter. When the transection was completed the caudal and rostral sections were separated and gel foam inserted between the divided ends. The wound was closed with continuous silk sutures. Chloroform anesthesia was then discontinued in order to hasten the return of reflex activity, the animals being maintained on positive pressure respiration. To conserve heat a heating pad or heat lamp was used in some cases but was generally found unnecessary. In cases of severe hypotension when the mean blood pressure dropped below 70 mm Hg neosynephrine was administered intramuscularly in 0.2 mg doses as needed to maintain blood pressure. This was frequently not necessary since the blood pressure usually stabilized between 80-100 mm Hg without using pressor agents.

A thermocouple was inserted into the side arm of the tracheal T-cannula and connected to a Grass Model 5 polygraph to measure intratracheal air flow. The thermocouple thus recorded a decreased temperature on inspiration and an

increased temperature on expiration. A pleural cannula was inserted into the right antero-lateral chest wall between the 4th and 5th intercostal space and connected to a Statham P23A pressure transducer. Changes in intrapleural pressure were then recorded on a Grass Model 5 polygraph. A pneumograph was placed around the abdomen and connected to a Statham P23A pressure transducer. Changes in abdominal circumference were measured as the pressure changed in the pneumograph. In two animals recordings were made of phrenic nerve activity. The left phrenic nerve was isolated in the neck. A bath of mineral oil heated to 39° C was maintained around the isolated nerve by suturing the adjacent muscle and skin flaps to form a pocket. The animal was placed inside a Faraday cage to decrease electrical interference. The phrenic nerve was divided to prevent motion artifacts and the perineureum and part of the nerve stripped away from the central end. The central end of the divided phrenic nerve was then placed on the points of a silver electrode and connected to a Grass EEG preamplifier. Recording by this technique was greatly limited by the frequency response of the pens and the amplification of the system.

Many different procedures were employed in order to initiate respiration, including sciatic nerve stimulation, hypercapnia, anoxia, strychnine sulfate and doxapram hydrochloride (AHR-619). The sciatic nerve was isolated in the thigh, divided and the central end of the divided nerve stimulated

via a Porter electrode. Many different parameters of stimulation were employed and electrical stimulation was tried periodically for 4-6 hours following completion of the spinal cord transection.

A second method used was ventilation of the animal with gas mixtures low in O_2 or high in CO_2. The different gas mixtures used were: 8-10% O_2 and 90-92% N_2; 20% O_2, 5% CO_2, 75% N_2; 10% O_2, 5% CO_2, 85% N_2. Total anoxia was also employed to initiate respiratory activity by interruption of positive pressure respiration. These procedures were tried intermittently for 4-6 hours following transection in order to initiate respiratory activity. The three procedures, perfusion with different gas mixtures, total anoxia, and sciatic nerve stimulation were employed both before and after the administration of 0.4-0.8 mg of strychnine sulfate intramuscularly.

A fourth method used to initiate respiratory activity involved the use of an experimental respiratory stimulant, doxapram hydrochloride or AHR-619. In this procedure 40-80 mg of AHR-619 were given intramuscularly 1-2 hours following completion of transection of the cervical spinal cord. If there was no response, this dose was again repeated in 30-45 minutes. Finally a combination of strychnine sulfate and doxapram hydrochloride was used simultaneously. In this procedure 0.2 mg of strychnine was administered one hour after completion of the surgical procedure. This dose of strychnine was repeated one hour later and followed in ten minutes by 30-40 mg of doxapram

hydrochloride. In some animals a third dose of 0.2 mg of strychnine was given three hours following completion of the transection and followed in ten minutes by an initial dose of 30-40 mg of doxapram hydrochloride.

CHAPTER III

EXPERIMENTAL RESULTS

More than 30 experiments were carried out using the different procedures to initiate respiratory activity. No attempt was made to stimulate respiratory activity until reflex activity of the animal returned following transection. To facilitate the return of reflex activity, chloroform anesthesia was discontinued immediately upon completion of transection of the spinal cord. The criteria for establishing the return of reflex activity were: return of the lid reflex, pupillary reflexes and peripheral deep tendon reflexes. Swallowing reflexes also returned and during the various procedures used to stimulate respiration the animal was often observed gasping. This activity, although not sufficient to change intrapleural pressure or abdominal circumference, would most likely have been sufficient to change intratracheal pressure if this were being measured. In those animals in which stimulation of the isolated central end of the sectioned sciatic nerve was employed to initiate respiration, no respiratory activity was observed. In those animals given 0.5 mg or more of strychnine sciatic nerve stimulation in some cases resulted in tonic

and/or clonic convulsive activity. Although small changes in intrapleural pressure were observed during the convulsive activity, there was little or no air flow and nothing to resemble normal respiratory activity.

In those experiments in which gas mixtures of low O_2 tension and other mixtures high in CO_2 content were used, no respiratory activity was observed even after continuous ventilation with these mixtures for thirty minutes. Likewise, total anoxia failed to stimulate respiratory activity. In animals given strychnine sulfate (0.4-0.8 mg) in which these same procedures were used no respiratory activity was noticed. Again convulsive activity was seen in those animals given sufficient doses of strychnine but at no time did this resemble normal respiratory activity.

In the third group of animals a combination of strychnine sulfate and doxapram hydrochloride (AHR-619)was used. These animals were given 0.2 mg of strychnine sulfate one hour after completion of transection; and the dose repeated one hour later. Following the second dose of strychnine, 30-40 mg of doxapram hydrochloride were administered intramuscularly. This procedure invariably resulted in respiratory activity independent of that of the respiratory pump; that is, although the animal was still on positive pressure respiration, it superimposed on this its own respiratory activity. Such a record is shown in figure 1 in which the top channel represents changes in abdominal circumference, the middle channel represents intratracheal air flow and the

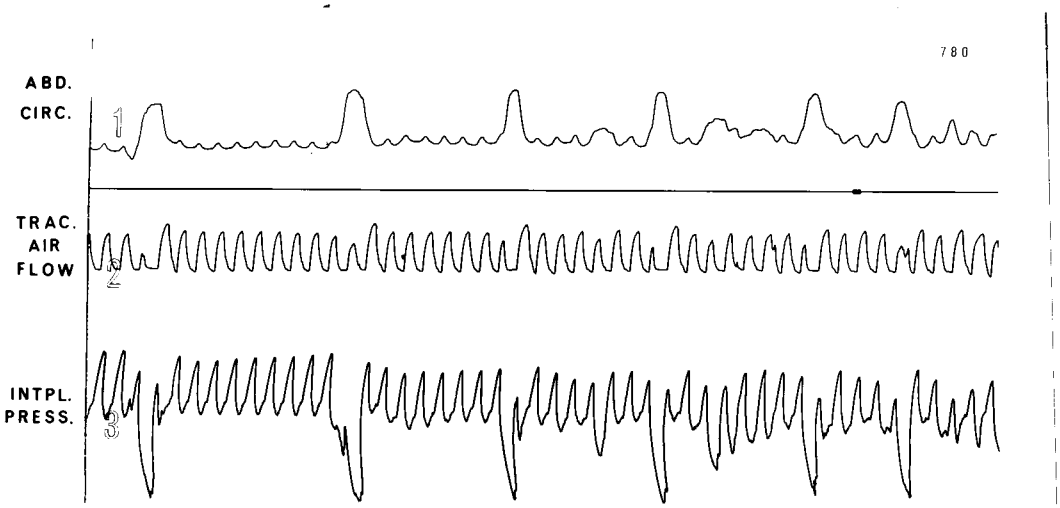

FIGURE ONE

FIGURE 1

SPONTANEOUS RESPIRATION SUPERIMPOSED ON RESPIRATORY PUMP

bottom channel shows intrapleural pressure. In this record the regular tracing obtained while the animal was on the respiratory pump was interrupted by the animal's own respiratory activity.

The character of this respiration appeared to differ from that normally seen prior to spinal cord transection. This respiration appeared to be primarily of diaphragmatic origin with little activity of the intercostal muscles noted. The irregularity of the tracing is due to the superimposition of the animal's own respiratory activity upon that of the positive pressure pump. The large negative deflections in the bottom tracing of figure 1 represent the spontaneous respiratory activity of the animal. This is in contrast to the regular symmetrical positive pressure tracings recorded in between the large negative deflections. These positive deflections represent the increases in intrapleural pressure resulting from a positive pressure artificial respiratory system, whereas when the animal breathes by itself, the intrapleural pressure becomes negative. In the top recording the large positive deflections represent the increase in abdominal circumference when the animal breathes on its own. The smaller undulations between these large positive deflections are a result of the respiratory pump. The great increase in abdominal circumference is a result of powerful sustained contractions of the diaphragm and as stated previously little or no activity of the intercostal muscles was observed.

Once respiratory activity was initiated artificial respiration was interrupted in order to determine the ability of the animal to maintain itself as well as to determine the effect of anoxia as a stimulant to respiration. The same procedure to initiate respiratory activity was employed as before, that is, 0.4 mg of strychnine followed by 30-40 mg of doxapram hydrochloride. When the animal was observed to superimpose his respiration upon that of the respiratory pump, the artificial respiration was discontinued and the respiratory activity of the animal recorded.

Figure 2 illustrates the fact that although the respiratory activity varied in depth, it tended to be rhythmic. The third channel of the tracing represents changes in intrapleural pressure. These negative pressure changes vary in degree but tend to be rhythmic. In the second channel of the recording respiration is being measured by an intratracheal thermocouple. In this recording inspiration of room air results in a decrease of temperature in the trachea which has been arranged in this tracing to give a negative deflection. In channel one abdominal circumference is measured. In this tracing a downward deflection of the record represents an increase in abdominal circumference. Again the respiration is noted to be primarily diaphragmatic with great increases in abdominal circumference upon inspiration. It is to be noted that in animals given more than 0.4 mg of strychnine, e.g., 0.6 mg, tonic muscular spasms of the trunk and extremities resulted interfering with recording

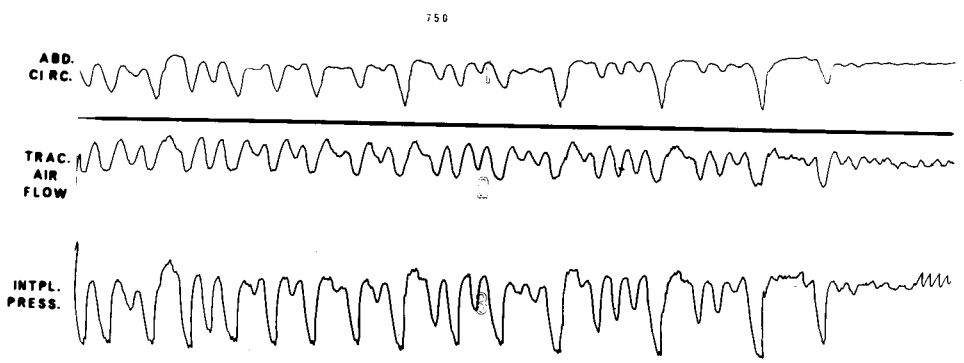

FIGURE TWO

FIGURE 2

THE INFLUENCE OF HYPOXIA ON RESPIRATORY RHYTHMICITY

procedures. In addition initiation of respiration using only doxapram hydrochloride and without strychnine was attempted in several animals. This procedure was effective in two animals and produced respiratory activity similar to that shown in figure 2 but of smaller magnitude. However, when using doxapram hydrochloride only, it was found necessary to use relatively larger doses, i.e., on the order of 60-80 mg and on many occasions increasing the dose greatly resulted in no observable respiratory activity.

Finally, experiments were conducted on two animals in which phrenic nerve action potentials were recorded. In this procedure following administration of strychnine and doxapram the left phrenic nerve was isolated in the neck and the central end of divided nerve lain across the points of a silver bipolar electrode. A simultaneous recording of abdominal circumference was made to correlate the nerve activity. A recording of this procedure is shown in figure 3. The large upward deflections in the top tracing represent increase in abdominal circumference. Channel two shows recordings of phrenic nerve action potentials as recorded by a Grass Model 5 Polygraph.

The early components of the bursts of phrenic nerve action potentials as observed by oscilloscopic monitoring were not able to be recorded on the Grass Model 5 polygraph due to the limitation of amplification obtainable in this system. The inability to record these early components explains the apparent onset of mechanical activity preceding electrical activity as shown in

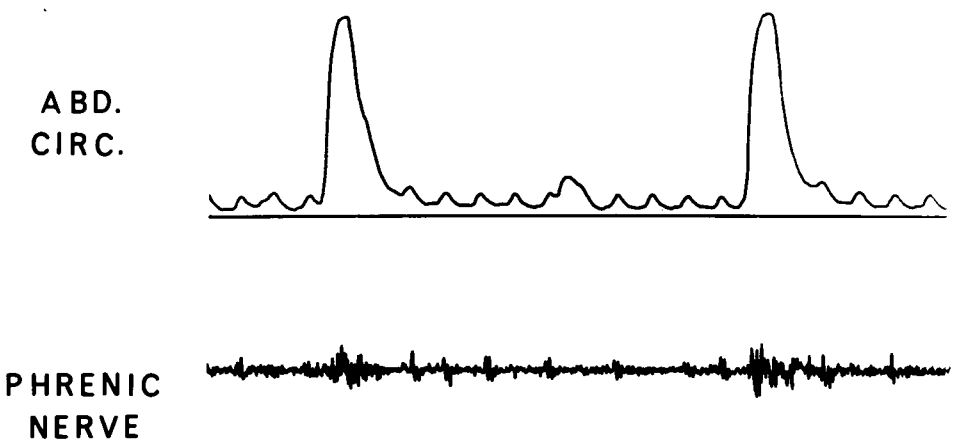

FIGURE THREE

FIGURE 3

PHRENIC NERVE ACTIVITY CORRELATED WITH CHANGES IN ABDOMINAL CIRCUMFERENCE

figure 3. Recordings were made from the central end of the sectioned phrenic nerve in order to eliminate potentials from afferent nerve fibers as well as to eliminate motion artifacts. The ability to record phrenic nerve activity as correlated with respiratory activity clearly demonstrates the diaphragmatic origin of this respiration.

CHAPTER IV

DISCUSSION

These experiments demonstrated that respiration can be elicited in animals with high cervical spinal cord transections. The recordings of intrapleural pressure, abdominal circumference and phrenic nerve action potentials clearly demonstrate that this respiration was of diaphragmatic origin. The objection of Porter to the work of Wertheimer and Langendorff that changes in intrathoracic pressure can be produced by contraction of the trapezius and sternocleidomastoid is not applicable to these experiments. Respiration was not measured by intrathoracic pressure tracings and both the sternocleidomastoid and trapezius muscles were divided by electrocautery in the surgical procedure. The frequent rhythmical swallowing reflex noticed previously may have been sufficient to change intrathoracic pressure recordings but had no effect whatsoever on intrapleural pressure. The inability of Porter to observe respiratory activity may be explained by several factors. The fact that he did a double transection at C1 and C5 may have interfered to some degree with the outflow of the phrenic nerves which in the dog is from C5, C6 and C7 (11) as

opposed to C2, C3, and C4 in the human. In addition he removed much of the spinal afferent input and did not employ any agents at all to facilitate initiation of respiratory activity. In the present experiments respiratory activity could not be initiated without a pharmacological stimulus. This is in contrast to the work of Wertheimer who stated that he was able to observe respiratory activity in adult animals without the use of strychnine. He also showed that respiratory activity once initiated could be stopped by the intravenous injection of bicarbonate (12). In our experiments CO_2 seemed to have only minimal effect on the observed respiratory activity. No experiments were carried out on newborn animals to ascertain whether respiratory activity could be observed in these animals without artificial stimuli as observed by Langendorff. In the experiments in which only strychnine was used, no activity resembling that of normal respiration was elicited. During convulsive activity, however, changes in intrapleural pressure and abdominal circumference occurred but these changes were neither regular nor effective from a ventilatory standpoint.

Also in these experiments it was not necessary to wait 4-6 hours as stated by Wertheimer in order to observe initiation of respiration. In nearly all experiments respiratory activity was observed 2 hours following completion of transection and might have been observe even sooner if the initiating procedures were carried out earlier. This may be in part due to the technique of transection. In Wertheimer's experiments his technique of spinal cord

transection consisted of a clean cut with a sharp knife. Although he gave no figures for the level of blood pressure observed post-operatively, he stated that the blood pressure was quite low. In our experiments transection of the cord by a single cut with a sharp scalpel resulted in post-operative mean blood pressures of 45-50 mm Hg. However, using the techniques of injection of the cord with small amounts of 1% Ravocaine followed by slowly teasing the cord apart over a period of 30-45 minutes, resulted in mean blood pressures post-operatively on the order of 80-100 mm Hg. In figure 4 a recording of blood pressure is shown before transection and also one hour following completion of spinal cord transection. In addition, in those animals in which the blood pressure fell below a mean pressure of 70 mm Hg, pressor agents were administered intramuscularly to maintain blood pressure. Also, it was found unnecessary to provide an artificial source of heat for the animal as this appeared to have no effect on the results obtained.

The character of the respiration observed bears comment as to its difference from that seen prior to transection. In all instances this consisted of a strong diaphragmatic contraction as evidenced by a much greater increase in the abdominal circumference as compared with normal quiet inspiration in a non-transected animal. This change in circumference can best be described as a prominent ballooning out of the abdomen. As regards the efficiency of the observed respiration, the ventilation was inadequate to maintain life for any

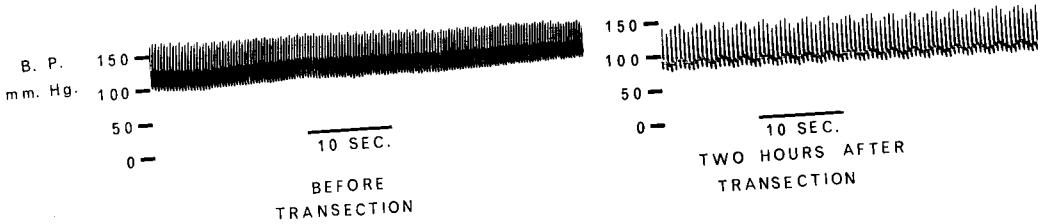

FIGURE FOUR

FIGURE 4

BLOOD PRESSURE BEFORE AND AFTER SPINAL TRANSECTION

length of time. This respiratory activity lasted from 3 to 5 minutes, but was not sufficient to maintain blood pressure; the pressure tending to drop precipitously after several minutes. Nevertheless, this respiration was effective in moving air and also was rhythmic in nature.

The most effective means of initiating respiratory activity was a combination of strychnine sulfate 0.4 mg and doxapram hydrochloride (AHR-619) 30-40 mg. In two animals respiration was initiated using doxapram by itself in relatively higher doses of 60-80 mg. Doxapram is known to be a potent respiratory stimulant believed to act primarily on the higher respiratory centers (13). These experiments suggest that it is also effective at the spinal level as shown by Funderbusk and Alpin (14). In our experiments little or no change in blood pressure was observed following intramuscular administration of doxapram in the spinal animal.

Although these experiments show that the isolated spinal cord is able to initiate rhythmic respiratory activity, the question arises as to whether the rhythmicity of this activity is a result of varying afferent input to the spinal cord, or whether the phrenic motorneuron cells have an inherent rhythmicity of their own. Adrian and Buytendijk (15) in 1931 recorded in vivo in the isolated brain stem of the goldfish, rhythmic potential waves of the same range of frequency as the respiratory movements. In these experiments they recorded rhythmic activity in the absence of sensory input. Likewise, Salmoiraghi and

Burns (16) in 1960 by ultramicroelectrode intracellular recordings showed that they were still able to record rhythmic nerve potentials following complete isolation of the pons and medulla. However, they also demonstrated that as the degree of isolation of the pons and medulla increased, the number of rhythmic potentials which they were able to record progressively decreased. They also were able to produce rhythmicity of cells by electrical stimulation of the caudal end of the isolated brain stem. In this experiment they applied a continuous stimulus to the caudal end of the isolated brain stem for 5 seconds, and following an interval of 10 msec, were able to record four rhythmic bursts of activity. They thus concluded that the rhythmicity of the "respiratory cells" is a result of the afferent input rather than an inherent property of the cells themselves.

The importance of afferent input to the spinal cord is demonstrated by the experiments of Ramos and Mendoza (17). These workers demonstrated that in rabbits with complete transection of the spinal cord, various stimuli, including manual compression of the abdomen or thorax, tactile stimulation or slight asphyxia resulted in marked increase in electrical activity of the intercostal muscles and diaphragm as recorded by electromyography. They also stated that these reflexes returned within 30 minutes following completion of the surgical procedure.

I conclude, therefore, that when the excitatory state of the isolated spinal cord is increased to a sufficient degree, either by increasing special facilitation by repeated somatic afferent stimulation or by pharmacological stimulation, the isolated spinal cord is capable of initiating rhythmic respiratory activity. Whether the rhythmicity of this activity is a characteristic of the phrenic motor nuclei or is a result of variation in afferent input is at the present time undecided. The inability of the respiratory activity to maintain life is most likely due to the loss of influences from the higher centers.

CHAPTER V

SUMMARY

It has been demonstrated that dogs with transection of the spinal cord at the level of C1 are able to initiate rhythmic respiratory activity effective in moving air. The most effective means found for initiating respiratory activity was the administration of .4 mg of strychnine intramuscularly followed by 30-40 mg of doxapram hydrochloride (AHR-619) intramuscularly. In two animals respiration was initiated using only doxapram hydrochloride in relatively higher doses on the order of 60-80 mg.

It was found that once respiration had been established, hypoxia acted as a stimulus in increasing the rate of respiration. Likewise, it was noted that the loss of reflex activity ("spinal shock") following transection of the spinal cord was of rather short duration with reflex activity returning in most cases within one hour. Also, the respiratory activity noted differed from that normally observed in intact resting animals in that it appeared to consist of much stronger and more maintained contractions of the diaphragm. Finally, this respiratory activity lasted for periods of 3-4 minutes but was not sufficient to maintain life for longer periods because the blood pressure

declined precipitously after a few minutes. The mechanism of rhythmicity as an intrinsic property of certain cells or as a result of changes in afferent input into the spinal cord has been discussed briefly.

BIBLIOGRAPHY

1. GALEN, cited by PITTS, R. F. Organization of the Respiratory Center, Physiol. Reviews 26: 609-630, 1946.
2. LOWRY, cited by PITTS, R. F. Organization of the Respiratory Center, Physiol. Reviews 26: 609-630, 1946.
3. BROWN-SEQUARD, cited by PORTER, W. T. The path of the respiratory impulse from the bulb to the phrenic nuclei, J. Physiol. 17: 455-485, 1905.
4. ROKITANSKY, cited by WERTHEIMER, E. Sur Les Centres Respiratoires De La Moelle Epiniere, Comptes Rendus Des Seances Et Memoires La Societe De Biologie. 38: 34-36, 1886.
5. LANGENDORFF, O. Studien Uber Die Innervation Der Athembewegungen, Archiv fur Physiol. 518-549, 1880.
6. WERTHEIMER, E. Sur Les Centres Respiratoires De La Moelle Epiniere. Comptes Rendus Des Seances Et Memoires La Societe De Biologie. 38: 34-36, 1886.
7. PORTER, W. T. The path of the respiratory impulse. From the bulb to the phrenic nuclei, J. Physiol. 17: 455-484, 1905.
8. HERMANN, H. Le Probleme Des Centres Respiratoires Medullaires. Arch. Internat. Physiol. 42: 232-237, 1936.
9. YOUNG, A. C. "Neural Control of Respiration," in RUCH, T. C., and FULTON, J. F. (eds.). Medical Physiology and Biophysics. Philadelphia: W. B. Saunders Company, 1960, pp. 813-828.

10. LAMBERTSEN, C.J. "Neurogenic Control of Respiration," in BARD, P. (ed.). Medical Physiology. St. Louis: The C.V. Mosby Company, 1961, pp. 613-632.

11. BRADLEY, O.C. Topographical Anatomy of the Dog. New York: The Macmillan Co., 1948.

12. WERTHEIMER, E. Sur Les Modifications De La Respiration Produites Por Les Injections Intraveineuses De Soude Chez Les Animaux A Moelle Cervicale Sectionnee. Comptes Rendus Des Seances Et Memoires La Societe De Biologie. 59: 668-669, 1905.

13. KATO, H. and BUCKLEY, J.P. Possible sites of action of the respiratory stimulant effect of doxapram hydrochloride, J. Pharm. and Exptl. Therapeutics 144: 260-264, 1964.

14. FUNDERBURK, W.H. and ALPHIN, R.S. Electrical changes in the CNS produced by a new respiratory stimulant, AHR-619, Fed. Proc. 21: 324, 1962.

15. ADRIAN, E.D. and BUYTENDIJK, F.J.J. Potential changes in the isolated brain stem of the goldfish, J. Physiol. 71: 121-135, 1931.

16. SALMOIRAGHI, G.C. and BURNS, B.D., Notes on mechanism of rhythmic respiration, J. Neurophysiol. 23: 14-26, 1960.

17. RAMOS, G. and MENDOZA, L. Spinal integration of respiration, Acta Physiol. Latino-Americana 9: 257-266, 1959.

APPROVAL SHEET

The thesis submitted by Peter Joseph Kane has been read and approved by three members of the faculty of the Graduate School.

The final copies have been examined by the director of the thesis and the signature which appears below verifies the fact that any necessary changes have been incorporated, and that the thesis is now given final approval with reference to content, form and mechanical accuracy.

The thesis is therefore accepted in partial fulfillment of the requirements for the Degree of Master of Science.

May 25, 1965
Date

Clarence N. Peiss
Signature of Advisor